ORIGINAL RESEARCH PAPER

Emergency Medicine

A CASE REPORT OF CLOFAZIMINE INDUCED HYPERPIGMENTATION

KEY WORDS: clofazamine, leprosy, pigmentation, mycobacterium leprae

Basavaraj. V	Pharma. D Student, Bldea's Ssm Pharmacy College, Vijayapur
Dr. Chaitra. Patil	Assistant Professorm , Department Of Emergency Medicine, Bldea's Shri. B.m.patil Medical College,Vijayapur
Shalini. B. Vagadurgi	Pharma D Student, Bldea's Ssm Pharmacy College,Vijayapur
Soniya Jain	Pharma. D Student, Bldea's Ssm Pharmacy College,Vijayapur
Samarth. P .K	Mbbs Student, Al-ameen Medical College,Vijayapur
Bharat. Burukule	Pharma. D Student, Bldea's Ssm Pharmacy College,vijayapur

ABSTRACT

Clofazimine is a class of riminophenazine anti-mycobacterial drug that was first synthesized in 1954.Clolfazimine is mainly used to treat leprosy(also known as Hansen's disease),dapsone-resistant lepromatous leprosy and leprosy complicated by erythema nodosum leprosum.Prolonged use of this drug may result in bioaccumulation of the drug in the body which leads to pigmentation in 10%-20% of cases.A 36-year old male patient came to the OPD with chief complaints of Raw red lesions associated with pain sensation over the body,swellling in both upper and lower limb extremities along with fever for one month.His past medication included citrizine, cefuroxime and rabeprazole.The medications were prescribed due to the patient's past history of mumps.The patient was then subjected to conservative drug regimen to combat the symptoms On further laboratory diagnosis after the treatment it was brought to the notice to the healthcare team that the patient was suffering from Borderline lepromatous leprosy with type I hypersensitvity reaction and was confirmedlater by laboratory diagnosis. At that point of time when the treatment began the patient started to show the adverse drug reaction due to clofazamine after a stretch of time.The clofazamine induced pigmentation of the skin should be thus made aware amongst the people who are in the healthcare industry to avoid any sort of overdose or drug related adverse effects

INTRODUCTION:-

Drug-induced skin pigmentation accounts for about 10-20% of all hyperpigmentation cases and can be triggered by a diverse range of medications, including NSAIDs, weakly basic drugs, heavy metals, and psychotropic drugs. Due to the fact that orally administered CFZ has been associated with massive intracellular accumulation of CLDIs and strong red pigmentation of macrophage-containing organs, we hypothesized that skin pigmentation is associated with CLDI bioaccumulation in macrophages[1].Clofazimine, a weakly basic lipophilic phenazine antibiotic, is a common cause of drug-induced pigmentation, particularly in patients with leprosy. Initially, it causes a pink to red discoloration of the skin, which is later replaced by typical dark brown pigmentation after a few months. The pigmentation persists throughout the period of drug intake and fades gradually after the discontinuation of clofazimine the exact nature of the material responsible for the discoloration is still a topic of debate. The initial reddish to reddish-blue color is thought to be due to the clofazimine (a reddish-blue aniline dye) accumulation. The dark brown color is due to drug-induced ceroid lipofuscinosis. It stains negative for melanin and iron. Although clofazimine can produce a generalized pigmentation, it usually involves leprosy-affected skin. The selective discoloration of the borderline tuberculoid leprosy plaque and sparing of other body parts is due to the selective uptake of clofazimine in the borderline tuberculoid plaque[2]. Regardless of the indication, whether it is for leprosy or multi-drug-resistant tuberculosis, studies that have evaluated the clinical efficacy and tolerability of CFZ have reported that skin pigmentation is the most common and dominating side effect that is observed in more than 94% of the patients . Patients may also experience ichthyosis or gastrointestinal symptoms, but at the normal dosage of 50 to 100 mg/d, no other major side effects have been reported[1]. Therapy with clofazimine has not been associated with elevations in serum enzymes during treatment and has not been linked to cases of clinically apparent liver injury. The combination of clofazimine, rifampin, and dapsone in multidrug therapy, however, is linked to cases of jaundice and hepatitis, which are most likely attributable to dapsone ("dapsone syndrome") and marked by fever, rash, eosinophilia and hepatic involvement (DRESS syndrome) typically arising within 8 weeks of starting the drug regimen. Dapsone induced liver injury can be severe and the mortality rate in cases with jaundice is as high as 25% to 33%. The liver injury usually resolves with stopping therapy and most patients have later tolerated restarting of clofazimine and rifampin. Thus, clinically apparent liver injury from clofazimine must be very rare, if it occurs at all[3].When Skin biopsy specimens from two lepromatous leprosy patients with dark brown pigmentation who were receiving long-term clofazimine therapy were studied. Ceroid-lipofuscin pigment was demonstrated inside macrophages that contained numerous phagolysosomes. These contained lipids and clofazimine that appeared as electron-lucent vacuoles and a lipofuscin pigment that was electron dense, granular, and lamellated. Although the presence of the drug in tissues contributed to the skin pigmentation, the main cause was a drug-induced, reversible ceroid lipofuscinosis[4]. Clofazimine is absorbed orally and tends to accumulate in tissues, boasting a very long half-life of approximately 70 days. It is excreted in small amounts through bile, urine, and sweat. This antibiotic is used to treat leprosy, multidrug-resistant tuberculosis, lepra reactions, and other mycobacterial infections. Clofazimine-induced pigmentation is reversible but takes months to years to clear after stopping the drug[5].

Case Presentation:-

A 36-year old male patient came to the OPD with chief complaints of Raw red lesions over the body associated with pain ,he also complained of swelling in all of the limb extremities along with fever since one month.The patient had a past history of mumps a month ago where he was on oral antibiotic medication for the month and the medications consisted of citrizine, cefuroxime and rabeprazole .Key vitals

like vital signs were within normal limits. Complete blood count,coagulation profile, urine examination, renal and liver function tests were also in normal limits.Thus the patient was then put through the new medications that included deaxamethasone (100mg),dapsone(100mg), prednisolone (40 mg) ,tab-calcimax(500mg),tab-dolo-650(650 mg) and finally clofazamine(50 mg) to overcome the current symptoms. When the patient was subjected to lab diagnosis like biopsy and slit stain smear the healthcare team of the hospital got to the see that the patient was diagnosed with borderline lepromatous leprosy with type I hyperensitvity reaction due to the use of clofazamine for while.After observing the leprosy being faded away the drugs provided were asked to stop whereby the pigmentation also reversed within a span of time.The patient is was told to visit hospital for examination periodically for any other adverse drug reactions persisted.The case is best described in pictures below:-

DISCUSSIONS:-

The patient exhibited skin hyperpigmentation caused by clofazimine, which was detectable through spectrophotometry and biopsy. Hyperpigmentation strongly impacted the social domain, indicating the intersectionality of disease and skin colour stigma, contributing to the social isolation of these patients. Health authorities should consider the negative impact of clofazimine on treatment adherence[6]. Significant effort has been devoted to developing clofazimine derivatives with enhanced pharmacokinetic and toxicity profiles. Researchers are focusing on less lipophilic compounds, which are expected to reduce tissue accumulation and discoloration while improving oral bioavailability.An attempt has also been made to alter the intrinsic colour, but this required modifications to the phenazine core, which eliminated antituberculosis activity[7]. Leprosy is a chronic disease caused by Mycobacterium leprae that affects the peripheral nervous system, skin, and other tissues. The primary medications used for treatment are dapsone, rifampicin, and clofazimine. Recommended by WHO for the treatment of leprosy, of which Clofazimine is known to pigment the skin[8]. Mycobacterium leprae has an affini ty for small unmyelinated nerve fibers, it flourishes best in the cooler areas of the body, and its growth is encouraged by the presence of dihydroxyphenylalanine (DOPA) in the surrounding tissues. In this respect, the anterior segment of the eye serves as a fertile soil where the organisms easily multiply. Corneal involvement in leprosy consists of transitory corneal nerve opacification, avascular keratitis, pannus, interstitial keratitis and corneal lepromata. Opacification of the corneal nerves is due to edema secondary to the multiplication of bacilli in or adjacent to the nerves, and cellular infiltration. Aggregation of inflammatory cells gives the appearance of beading[9].

CONCLUSION:-

Overall, our results suggest that skin hyperpigmentation should be anticipated with oral or systemic administration of clofazimine, as the drug tends to accumulate in the skin after absorption from the systemic circulation.To minimize CFZ-induced skin hyperpigmentation, the most effective approach would be to reduce drug concentrations in circulation.This can be achieved through local administration and controlled-release formulations. Current evidence supports the use of clofazimine-containing regimens, which demonstrate greater efficacy compared to standard treatment regimens. The use of clofazimine can possibly shorten the length of MDR-TB and leprosy treatment with typically minor adverse effects, with serious adverse effects being rare. However, the optimal dose and duration of treatment with clofazimine need further investigation[10]. Periodic investigations must be done inorder to keep a check on the pigmentation of the skin.

REFERENCES:-

1. Murashov, M. D., LaLone, V., Rzeczycki, P. M., Keswani, R. K., Yoon, G. S., Sud, S., Rajeswaran, W., Larsen, S., Stringer, K. A., & Rosania, G. R. (2018). The Physicochemical Basis of Clofazimine-Induced Skin Pigmentation. The Journal of investigative dermatology, 138(3), 697–703. https://doi.org/10.1016/j.jid.2017.09.031
2. Behera, B., Palit, A., Sethy, M., Nayak, A. K., Dash, S., & Ayyanar, P. (2021). Dermoscopic features of clofazimine-induced pigmentation in a borderline tuberculoid leprosy plaque. Indian Journal of Dermatology Venereology and Leprology, 88, 85–87. https://doi.org/10.25259/ijdvl_1421_20
3. LiverTox: Clinical and Research Information on Drug-Induced Liver Injury. (2017). Clofazimine [Report]. In LiverTox. National Institute of Diabetes and Digestive and Kidney Diseases. https://www.ncbi.nlm.nih.gov/books/ (Original work published 2017)
4. Job, Charles K. Yoder, Leo Jacobson, Robert R Hastings, Robert C(1989).Skin pigmentation from clofazimine therapy in leprosy patients: A reappraisal Journal of the American Academy of Dermatology 236-24. https://doi.org/10.1016/0190-9622(90)70204-U
5. Karnan, A., & Ledwani, A. (2024). Clofazimine-induced skin pigmentation. The Pan African medical journal, 47, 86. https://doi.org/10.11604/pamj.2024.47.86.42513
6. Nogueira, A. S., Garcia, M. a. C., Da Silva, M. B., Da Costa, P. F., Frade, M. a. C., Salgado, C. G., & Barreto, J. G. (2024). Clofazimine‐induced cutaneous hyperpigmentation as a source of stigma in the treatment of leprosy: A cross‐sectional study. Tropical Medicine & International Health, 29(4), 327–333. https://doi.org/10.1111/tmi.13977
7. Stadler, J. a. M., Maartens, G., Meintjes, G., & Wasserman, S. (2023). Clofazimine for the treatment of tuberculosis. Frontiers in Pharmacology, 14. https://doi.org/10.3389/fphar.2023.1100488
8. Philip, M., Simi, P., & Samson, J. (2012). Clofazimine-induced hair pigmentation. International Journal of Trichology, 4(3), 174. https://doi.org/10.4103/0974-7753.100088
9. Pavesio, C. B., Gelber, R., & Ostler, H. B. (1994). Pigmented corneal nerves in leprosy patients treated with clofazimine. Arquivos Brasileiros De Oftalmologia, 57(4). https://doi.org/10.5935/0004-2749.19940028
10. Nugraha, R. V., Yunivita, V., Santoso, P., Aarnoutse, R. E., & Ruslami, R. (2021). Clofazimine as a Treatment for Multidrug-Resistant Tuberculosis: A review. Scientia Pharmaceutica, 89(2), 19. https://doi.org/10.3390/scipharm89020019.